Controversies in Vitreoretinal Surgery:

Is Vitrectomy an Appropriate Treatment for DME in 2014?

These articles are based on the debate-style presentations at the American Academy of Ophthalmology Retina Subspecialty Day in New Orleans November 15-16, 2013. The arguments presented by the authors, affirmative or negative, were assigned to them and do not necessarily reflect their own opinions or practices.

Vitrectomy for DME: Pro

By Tarek S. Hassan, MD

In the accompanying "con" article in this debate, Julia A. Haller, MD, will attempt to cite numerous reasons to support the argument that, in the current era, vitrectomy has no significant role in treating diabetic macular edema (DME). Those who do not favor routine use of this surgical approach to DME say that vitrectomy does not consistently reduce macular thickening; that it does not lead to improved visual acuity; that it may work only in eyes with vitreomacular traction; that numerous series have shown no consistent benefit of vitrectomy; that the only major prospective clinical trial of note evaluating vitrectomy for DME was underwhelming in its support of vitrectomy; and that the availability of anti-VEGF and steroid intravitreal injections eliminates the need for vitrectomy in most eyes.

In my opinion, the evidence clearly demonstrates that none of those things is true, and that vitrectomy works for DME.

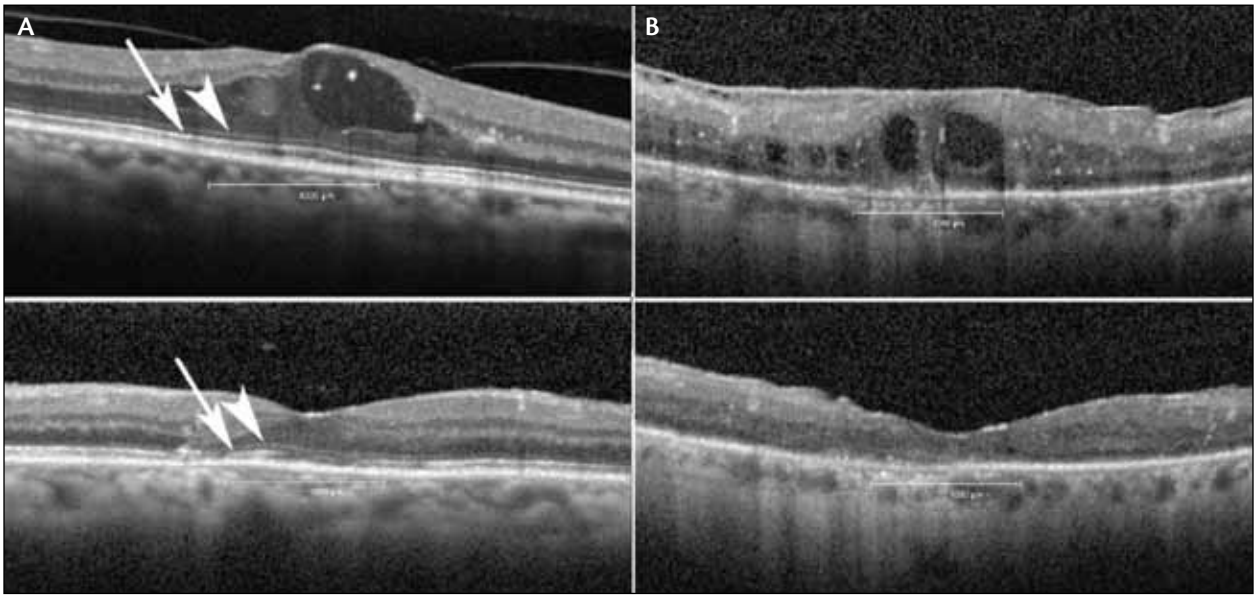
In the era before the advent of steroid and anti-VEGF intravitreal injections, the only tool ophthalmologists had to treat DME that was refractory to laser was vitrectomy. As a result, we have 20 years' worth of published data that demonstrate the successful use of vitrectomy in the treatment of DME. Vitrectomy, with membrane peeling as performed in these studies, may have included removal of the posterior hyaloid with or without peeling of the internal limiting membrane (ILM), concurrent panretinal photocoagulation (PRP), and intravitreal triamcinolone injection. Multiple authors reported that these treatments could relieve posterior hyaloidal traction (also known as taut hyaloid syndrome) and lead to improved visual acuity and reduction or resolution of DME in some eyes refractory to other treatments.

In the period before injections became popular, from 1992 to 2005, no fewer than 15 studies were published documenting the positive results of vitrectomy for DME.[1-15] The authors of these studies reported improvements of 2 or more lines of visual acuity in 38% to 92% of eyes and resolution of DME in 45% to 100% of eyes. These studies included eyes in which posterior hyaloidal traction was clearly clinically visible and/or demonstrated on optical coherence tomography (OCT), as well as those in which it was suspected but not seen.

With the use of vitrectomy as performed in these studies, results like those seen in Figure 1 were achieved. Visual and anatomic improvements were significant, potentially seen early, and generally quite long-lasting.

HOW DOES IT WORK?

Vitrectomy is thought to treat DME through multiple mechanisms. Vitrectomy relieves anteroposterior vitreoretinal traction, creating a posterior vitreous detachment (PVD), and it has long been known that PVD is associated with reduction or resolution of DME.[16,17] But vitrectomy also relieves tangential traction by the removal of contractile vitreous and retinal pigment epithelium (RPE) cells within the posterior hyaloid that



Courtesy Maurice Landers, MD

Figure 1. Significant visual and anatomic improvements have been seen after vitrectomy for DME. Preoperative visual acuity of 20/80 (top) improved to 20/25 (bottom) postoperatively (A). Visual acuity of 20/200 (top) improved to 20/160 (bottom) postoperatively (B).

contribute to the edema.

In addition, the ILM that is removed during vitrectomy is actually pathologic tissue that contains increased levels of fibronectin, laminin, and types 1, 3, 4, and 5 collagen. The ILM in DME is abnormally thick—2.5 times thicker than ILM removed in a macular hole case—and that thickened condition alters membrane function. The inner monolayer of ILM is also contractile; immunohistochemistry studies show that there is smooth muscle immunoreactivity of this tissue.

Vitrectomy removes numerous vasoactive and vasodamaging factors that are elevated in DME eyes compared with controls, and it increases oxygenation in the vitreous cavity by up to 10 times, with a potentially long-acting effect.[18] Intraoperative PRP at the time of vitrectomy can reduce peripheral ischemia and thereby decrease levels of VEGF and other vascular permeability factors.

Through multiple mechanisms, we see that vitrectomy almost always thins the macula. Maurice Landers performed a literature review of 29 series published between 2003 and 2012, both retrospective (20; n=1012) and prospective (9; n=869). In the 1881 eyes included in these series, there was a more than 200 µm mean decrease in mean foveal thickness during the course of follow-up (M. Landers, personal communication).

MACULAR THINNING AND VISUAL OUTCOMES

The "cons" will say that vitrectomy may thin the retina in some of these trials, but it does not improve visual acuity. They will cite the paradoxical response seen in 1 prospective trial,[19] in which retinal thinning occurred after vitrectomy but in some eyes the visual acuity was worsened.

However, we must keep in mind that in prospective pivotal clinical trials to assess drugs that treat DME or macular edema associated with retinal vein occlusion, strong correlations have been reported between reduced macular edema and improved vision. What is the difference? Trials for approval of new pharmaceutical entities have well-controlled inclusion criteria, and eyes with poor prognosis are not enrolled. Most studies of vitrectomy for DME are not like that.

Before the advent of intravitreal injections, vitrectomy was done much earlier in the course of DME than it is today. The role of traction was considered earlier, as there was no other treatment available for eyes refractory to laser. Therefore, eyes with better prognosis, with less irreversible macular damage and less macular ischemia, were taken to surgery, and as a result these patients experienced better outcomes and improved vision.

In more recent series and studies, vitrectomy has been performed in eyes that have experienced repeated injections and laser and have had a long duration of chronic DME without significant improvement. In these eyes with

a poorer prognosis, irreversible macular damage at the photoreceptor level, and macular ischemia, consistent improvement of visual acuity should not be expected.

In fact, we can now see that DME eyes with better prognosis—with intact photoreceptors—tend to achieve better visual acuity after vitrectomy. OCT now affords anatomic predictors of the visual acuity response to vitrectomy in DME. Sakamoto et al[20] reported that better final visual acuity is achieved in eyes with a complete inner segment/outer segment (IS/OS) junction. Yanyali and colleagues[21] found that integrity of the external limiting membrane and IS/OS lines on OCT strongly correlated with better postoperative visual acuity recovery. These factors are related to the duration of edema prior to vitrectomy.

ALL EYES NOT EQUAL

In assessing the published record, it must be borne in mind that all eyes with DME are not equal. For results to be compared across trials in order to truly assess the benefit of vitrectomy of DME, it is important to have established parameters. Investigators must define patient characteristics; define and determine what is "traction"; define and determine the amount of macular ischemia, RPE atrophy, and choroidal ischemia present; and define the surgical parameters and techniques to be used. The problem is that with so many variables left uncontrolled, studies are rarely—possibly never—truly comparable.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluated the effect of vitrectomy for the treatment of DME in eyes with at least moderate vision loss and vitreomacular traction.[22] This prospective cohort study included 87 eyes recruited from 35 sites. The presence of vitreomacular traction was based on investigator assessment only, and vitrectomy was performed "according to the investigator's usual routine." The only guidelines in the methods section were that the patient had to have 3 sclerotomies, the posterior hyaloid was peeled, ERMs were removed, and the periphery was examined.

The results showed that vitrectomy worked for some eyes and not others. Retinal thickening was significantly reduced in most eyes, and visual acuity improved by 10 letters or more in 38% of eyes and decreased by 10 letters or more in 22% of eyes. There was a low rate of operative complications.

The problem with this study is that it was a nonstandardized, nonrandomized, uncontrolled, prospective data collection study only. That is to say, it was a survey. There was no standardization of indications for surgery, no definition of surgical procedure or techniques; surgeons simply reported their outcomes.

> Injections of anti-VEGF agents and triamcinolone can be effective against DME, but there are risks involved in viewing such treatments as too much of a panacea.

Substantive conclusions on vitrectomy for DME cannot be derived from this survey. In fact, the true value of the DRCR.net trial is that it demonstrated the need for a well-controlled, standardized prospective trial to investigate modern vitrectomy using small-gauge instrumentation for DME.

WHAT ARE THE OPTIONS?

In the era of intravitreal injections, what is the retina specialist to do for a patient with persistent DME and poor or worsening visual acuity despite current therapy? If vitrectomy for DME is not an option, the clinician will most likely continue to inject, perhaps adding focal or scatter laser.

However, persistent injections, if they do not lead to improvement, are likely to be harmful to long-term visual recovery. A relentless schedule of injections, in the face of little to no response, delays progression to other therapies (such as vitrectomy) and can allow permanent macular damage to occur in the meantime.

Continued injection is also expensive compared with vitrectomy. Friedman[23] estimated that, if the protocols of recent published pivotal trials were followed, injection of approved anti-VEGF agents for 2 years would cost $26 000 to $27 000 per patient.

Safety is also a potential concern. The cumulative risk of endophthalmitis after 20 to 40 injections is approximately 1%. There is no doubt that injections of anti-VEGF agents and triamcinolone can be effective against DME, but there are risks involved in viewing such treatments as too much of a panacea.

CONCLUSIONS

Those who say vitrectomy does not work for DME ignore the evidence gathered from many case series conducted in multiple centers over many years. Additionally, critics of vitrectomy for DME are, in my opinion, placing too much faith in negative vitrectomy trials that were not well controlled for important clinical and surgical parameters. It is important to consider

all aspects of the complex pathophysiology of DME. In not doing so, those who contend that vitrectomy has no place in the treatment of DME are missing its appropriate place in the treatment regimen.

Physicians must keep their options open and not be excessively devoted to intravitreal injections and laser as the only options for the treatment of DME. Vitrectomy should be thought of as part of a regimen that includes injections, lasers, and systemic medical control. It is important to identify the appropriate place for vitrectomy in that treatment paradigm so that we can use all available tools and potentially get the best possible outcomes.

Vitrectomy works for DME. All arguments made to the contrary do not hold up to any significant scrutiny.

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Vitrectomy for DME: Con

By Julia A. Haller, MD

In 2014, vitrectomy has only a limited role in the treatment of most cases of nontractional diabetic macular edema (DME).

This is because there has been an evolution in the past 3 decades of diabetic therapy. In an earlier era, the only tools available to the ophthalmologist for treatment of DME were destructive thermal laser and invasive surgery. Today we see the diabetic eye in the context of systemic health, and we try to treat it with as little collateral damage as possible—to nudge it back to health, rather than bludgeon it, so to speak.

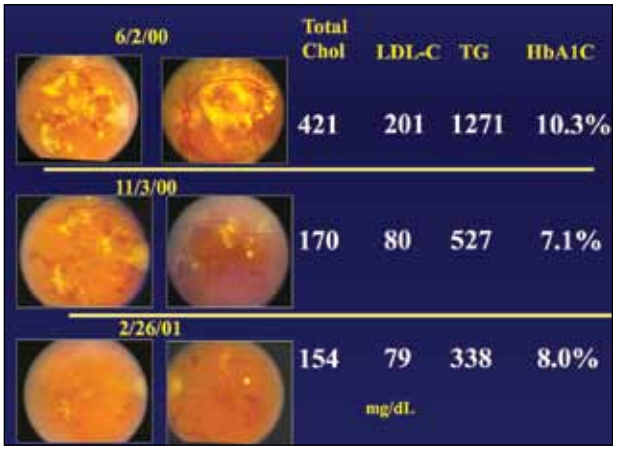
The treatment algorithm for DME today may involve numerous options, starting with metabolic control and proceeding to injection of anti-VEGF agents, use of focal laser, scatter laser, and perhaps steroid injection or some other adjustment of the pharmacologic approach (with a different agent or more frequent application) before finally arriving at vitrectomy. This option is generally reserved for very rare cases, usually those with abnormalities of the vitreoretinal interface.

Today we talk to patients in a much more sophisticated way about metabolic control, which includes not only monitoring of hyperglycemia, hypertension, and lipid levels, but also awareness of a patient's smoking status and diagnoses such as depression, problems with sleep apnea, and eating disorders. Care of the diabetic patient involves collaboration with a medical team that may include a diabetologist and/or internal medicine specialist.

MODERN TREATMENT APPROACHES

Metabolic control is the essential first step in care of the patient with DME. Improvement in DME has even been shown to occur with metabolic control alone, as shown in the case illustrated in Figure 1.[1]

When confronted with an eye with DME with vascular leakage and some ischemia, as seen in Figure 2, rather than treat with an invasive or destructive approach, today's ophthalmologist will take a stepwise course. First-line therapy would include intravitreal injections with 1 of the available anti-VEGF or steroid options. The next step might be focal laser, especially in eyes with extrafoveal



Reprinted with permission for Elsevier from: Cusick M, Chew EY, Chan CC, Kruth HS, Murphy RP, Ferris FL, III. Histopathology and regression of retinal hard exudates in diabetic retinopathy following reduction of elevated serum lipid levels. *Ophthalmology*. 2003;110(11):2126-2133.

Figure 1. DME treated with metabolic control alone, with remarkable reduction in macular edema over the course of 8 months.

leakage, hard exudates, and/or circinate rings.

In his accompanying article defending the use of vitrectomy to treat DME, Tarek S. Hassan, MD, cites numerous studies published in the era before intravitreal injections were common, which describe various levels of success with vitrectomy for DME. We now have 3-year follow-up data from a study by the Diabetic Retinopathy Clinical Research Network (DRCR.net) assessing pharmacotherapeutic treatments for DME in a randomized, prospective setting.[2-4] This trial is nothing like those old studies cited by Dr. Hassan, which in many cases included no optical coherence tomography (OCT) assessment, and were, in general, small retrospective series without any control group.

This carefully designed and executed study by DRCR.net has demonstrated that good anatomic and visual acuity results can be achieved with the use of intravitreal injections. We also know that anti-VEGF drugs not only treat patients' DME, but also improve their diabetic retinopathy.[2-4]

If an incomplete response to intravitreal therapy is achieved, there are multiple ways to titrate treatment, including injecting more frequently, increasing the dosage, trying another agent, or adding focal laser or panretinal photocoagulation (PRP) judiciously. Again, vitrectomy is far down the list of options and, again, generally used only in isolated cases in which there may be vitreoretinal interface abnormalities.

Even eyes that are refractory to treatment do not always need vitrectomy. For example, Figure 3 shows an ischemic eye that has recalcitrant DME despite multiple bevacizumab injections and both focal laser and PRP. Rather than rushing this patient to the operating room, a dexamethasone intravitreal implant (Ozurdex, Allergan) was given, and the patient's visual acuity improved to 20/40 with a nice anatomic result within 6 weeks.

VITRECTOMY FOR DME STUDY

The DRCR.net evaluated the use of vitrectomy for DME in a prospective multicenter cohort study.[5] Data were collected on 241 individuals who underwent vitrectomy as primary treatment for DME. The primary cohort included 87 eyes with DME and vitreomacular traction based on investigator assessment. Following vitrectomy, retinal thickening was reduced in most eyes. Mean central subfield thickness decreased by 160 µm at 6 months; 43% of eyes had complete resolution of edema, and 68% had at least a 50% reduction.

Unfortunately, however, in the primary cohort—in these eyes with vitreomacular traction, which one might think would have the best results—the visual acuity results were disappointing. The authors concluded that, while 28% to 49% of eyes similar to those in the study were likely to have improvement of visual acuity, 13% to 31% were likely to experience worsening.

Why was this disappointing result seen? Many factors could be at work. A subset analysis showed that peeling of the epiretinal membrane (ERM) and internal limiting membrane (ILM) was associated with thinning of the retina. Perhaps, however, additional risk was introduced

Figure 2. An eye with vascular leakage and ischemia. Rather than an invasive or destructive approach, treatment today would proceed in stepwise fashion, with first-line therapy including intravitreal injections.

Courtesy of Homayoun Tabendeh, MD

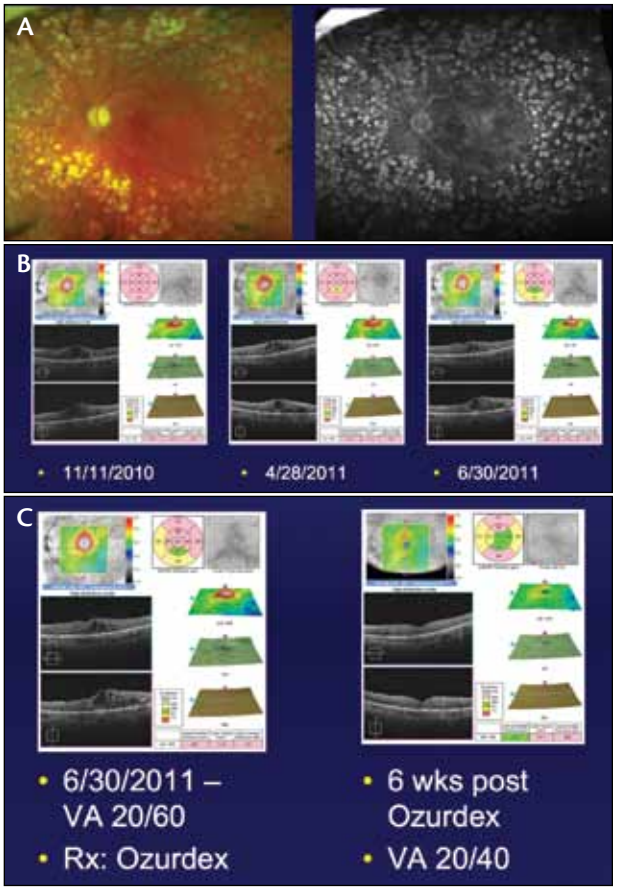


Figure 3. An ischemic eye (A) that has recalcitrant DME despite multiple bevacizumab injections and both focal laser and PRP (B). Six weeks after dexamethasone intravitreal implant, the patient's visual acuity improved to 20/40 with a good anatomic result (C).

by peeling these delicate membranes, including the footplates of the Mueller cells, in eyes with ischemia and diabetes.

In addition, the complications of vitrectomy, although rare, are unacceptable in the treatment of DME when, today, there are so many alternative treatment options. Endophthalmitis, retinal detachment, and proliferative vitreoretinopathy can have devastating consequences. In fact, one could even argue that the increase in nuclear sclerosis that is a predictable side effect of vitrectomy surgery is unacceptable when other therapeutic approaches are available.

SUMMARY

Treatment of DME has evolved in the past 3 decades, away from the bludgeons of invasive surgery and heavy thermal laser. We now attempt to nudge the eye toward health. Today we must give a thumbs-down to vitrectomy for DME. In light of the other treatment options available, it is excessive, and it is almost never needed. New therapies on the horizon may further increase the options for safe and effective treatment of DME—including the intriguing possibility of performing pharmacologic vitrectomy in these eyes. ■

The complications of vitrectomy, although rare, are unacceptable in the treatment of DME when, today, there are so many alternative treatment options.

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